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REVIEW

Extending the duration of response in chronic myelogenous leukemia: targeted therapy with sequential tyrosine kinase inhibitors

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Abstract Tyrosine kinase inhibitors (TKIs) are the mainstay for treatment of chronic myelogenous leukemia (CML). Imatinib was the first TKI approved for use in CML, but resistance to this therapy has emerged as a significant issue, and second-line options are often necessary. Increased-dose imatinib may elicit responses in some patients, but clinical evidence suggests only a minority experience sustained benefit. The second-generation TKIs, dasatinib and nilotinib, have demonstrated efficacy in patients resistant or intolerant to imatinib. Changes in therapy, with the aim of inducing durable response, should occur promptly after imatinib failure is identified as all agents are more effective in chronic phase disease than in later stages. Selection of second-line agents should be driven by efficacy and safety: dasatinib may be more effective in patients with P-loop or F359C mutations; nilotinib may be more effective in those with F317L mutations.

Keywords Dasatinib · Imatinib · Nilotinib · CML · Philadelphia chromosome · BCR-ABL

Introduction

Chronic myelogenous leukemia (CML) is characterized by the presence of the Philadelphia (Ph) chromosome which encodes the BCR-ABL fusion protein, the causative molecular aberration in the pathogenesis of the disease [1]. CML is usually diagnosed in the chronic phase (CP), and, if left untreated, the disease will progress to an accelerated phase (AP) and, ultimately, to a terminal blast phase (BP) within 3–5 years [2] (Table 1). Ph is also present in a subpopulation of patients with acute lymphoblastic leukemia (Ph^+ALL).

Tyrosine kinase inhibitors (TKIs) which target BCR-ABL are the mainstay for treatment of CML. Imatinib was the first approved BCR-ABL-targeted therapy for use in CML, and has substantially changed the treatment and outcomes associated with this disease. Before the introduction of such TKIs, 5-year survival rates with interferon treatment or chemotherapy were 57 and 42%, respectively [6]. Imatinib therapy is associated with a 5-year overall survival rate of 89% [7]. Nonetheless, resistance has also emerged as a significant clinical issue with this agent and effective second-line and beyond treatments continue to be needed and developed. Two second-generation TKIs have been approved for the treatment of patients with imatinib resistance or intolerance. Dasatinib was approved for the treatment of patients with CML that have resistance or intolerance to imatinib. Nilotinib was approved for the treatment of patients with CP or AP CML who have failed prior treatment. In the age of targeted TKI therapy, it is key to select the appropriate agent at the appropriate juncture for each patient, the aim being to achieve long-term, durable responses with minimal toxicity. Here, we discuss the current treatment options for patients with CML that have failed imatinib and evaluate the important considerations when designing treatment algorithms.

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First-line imatinib

In the pivotal phase III International Randomized Study of Interferon and STI571 (IRIS) trial, imatinib (400 mg/day)

Table 1 Definitions of accelerated phase and blast crisis CML [3–5]

	World health organization criteria	International bone marrow transplant registry criteria
Accelerated phase	• Peripheral blood and/or marrow blasts 10–19% • Peripheral blood basophils ≥20% • Persistent thrombocytopenia (<100 × 10^9/L) or thrombocytosis (>1,000 × 10^9/L) unresponsive to therapy • Progressive splenomegaly and increasing white blood cell count unresponsive to therapy • Cytogenetic evidence of clonal evolution	• Peripheral blood or marrow blasts ≥10% • Peripheral blood basophils and eosinophils ≥20% • Anemia or thrombocytopenia unresponsive to hydroxyurea/busulfan • Persistent thrombocytosis • Progressive splenomegaly • Clonal evolution • Peripheral blood or marrow blasts and promyelocytes ≥20% • Leukocyte count difficult to control with hydroxyurea/busulfan • Rapid leukocyte doubling time (<5 days) • Development of myelofibrosis
Blast crisis	• Peripheral blood or marrow blasts ≥20% • Extramedullary blast proliferation • Large blast foci/clusters in bone marrow biopsy	• Peripheral blood or marrow blasts ≥20% • Extramedullary leukemic cell infiltrates

showed superior activity compared with the previous front-line therapy, interferon-a plus low-dose cytarabine, in patients with newly diagnosed CP CML. The estimated rates of major cytogenetic response (MCyR; Table 2) at 18 months were 87 and 35% with imatinib and interferon, respectively. Complete cytogenetic response (CCyR; Table 2) rates were 76% in the imatinib group and 15% in the interferon group ($P < 0.001$) [9]. At 60 months, 67% (368/553) of patients treated with imatinib achieved a CCyR, and overall survival was 89% [7].

Imatinib also has activity in patients with advanced stage CML, but the therapeutic advantages here are modest: MCyR rates recorded in phase II studies in patients with AP/BC CML were 16–24% [10, 11]. Three-year overall survival rates for patients following imatinib failure have been reported as 72% for patients with CP CML, 30% for patients with AP CML, and 7% for those with BC disease [12]. These data underline the importance of preventing disease progression.

A recently published retrospective study in patients with CP CML receiving first-line imatinib (400–800 mg/day) has provided direct evidence that durability of response predicts patient outcome [13]. In this study of 276 patients, maintenance of a CCyR or major molecular response (MMR) for ≥12 months was significantly ($P \leq 0.01$) associated with improved progression-free survival (PFS) compared with responses lasting less than 12 months. In total, 78% of patients maintained a CCyR for ≥6 months, this figure falling to 71% at ≥12 months, and 54% at ≥24 months. Similarly, the percentages of patients maintaining a MMR for ≥6, ≥12, and ≥18 months were 54, 43, and 32%, respectively. In patients receiving the currently approved first-line dosage of 400 mg/day alone, the rates of CCyR and MMR durable for 12 months or more were lower; 59 and 39%, respectively.

Imatinib resistance

Despite the impressive activity associated with imatinib therapy, resistance has emerged as a serious clinical issue. Resistance to imatinib is defined as either primary, where patients are refractory to imatinib treatment, or secondary, in which a previously achieved response is lost. In the IRIS trial, approximately 25% of patients were reported to exhibit some degree of primary resistance to imatinib: an

Table 2 Criteria for hematologic, cytogenetic, and molecular responses [8]

Monitoring technique	Category of response	Criteria
Hematologic	Complete	White blood cell counts <1 × 10^9/L plus normal differential; platelet count <450 × 10^9/L; non-palpable spleen
Cytogenetic	Minor	Ph^+ metaphases = 36–95%
	Major	Ph^+ metaphases = 0–35%
	Complete	Ph^+ metaphases = 0%
Molecular	Major	BCR-ABL/ABL ratio <0.10%, or >3-log decrease from baseline

estimated 5% of patients failed to achieve a complete hematologic response (CHR) at 3 months, 22% failed to achieve any cytogenetic response at 6 months, 23% failed to achieve at least a partial cytogenetic response (PCyR; Table 2) at 12 months, and 24% failed to achieve a CCyR at 18 months [7, 9, 14]. Secondary resistance was also evident. After 60 months of follow-up, the estimated relapse rate was 17% and progression to AP or BP occurred in 7% of patients [7]. In a second study, intent-to-treat analysis revealed that the probability of remaining in MCyR at 5 years is 63% (i.e., 37% of patients required alternative treatment within 5 years of diagnosis) [15]. Similarly, a large retrospective analysis revealed resistance or intolerance to imatinib in 45% of patients [16]. Therefore, there is a strong clinical need for further treatment options.

Several mechanisms are likely to underlie the development of imatinib resistance. One of the most established causes of imatinib resistance is the acquisition of point mutations in the kinase domain of BCR-ABL [10]. BCR-ABL mutations have been reported at a frequency in the range of 42–90% among patients with secondary imatinib resistance [17–19]. Mutations emerge more frequently among patients with advanced disease compared with those with CP disease, and the frequency increases with disease duration [20]. Furthermore, the presence of point mutations at baseline has been shown to predict loss of CCyR on imatinib therapy [15].

Over 40 different imatinib-resistant mutations have been identified to date [21]. These generally fall within four regions of the ABL kinase domain, including the ATP binding loop (P-loop), the contact site (e.g., T315 and F317), the SH2 binding site (e.g., M351), and the A-loop [22]. The different BCR-ABL mutations emerge at varying frequencies which can differ according to the stage of the disease [21]. The most frequently occurring mutations (30–40%) are within the P-loop. P-loop mutations confer high levels of resistance to imatinib and are associated with poor prognosis [23]. The second most frequently observed mutation is T315I [23]. This single amino acid substitution renders BCR-ABL-expressing cells insensitive to imatinib as well as other clinically available tyrosine kinase inhibitors [24]. Of note, these mutations decrease the efficacy of TKIs in CML, but do not necessarily predict an increase in the aggressiveness of the clone, and patients with mutations may have an indolent course [25].

A more recently implicated cause of imatinib resistance is the constitutive activation of downstream signaling molecules (e.g., SRC family kinases or SFKs). SFK-mediated phosphorylation (i.e., activation) of BCR-ABL is required for full oncogenic activity [26]. Transfection of myeloid leukemia cells with kinase-defective HCK has been shown to block BCR-ABL-related cellular transformation [27].

Further studies indicate that SFK activation is present in imatinib-resistant CML and that such activation may be targeted therapeutically. Overexpression of the SFKs, LYN and HCK, have been reported in CML cell lines exhibiting BCR-ABL-independent imatinib resistance, and SFK inhibition in these cells resulted in growth inhibition [28, 29]. A recent report has shown that FYN (another SFK) is up-regulated by BCR-ABL and that FYN expression correlated to the stage of the disease, being significantly increased in blast crisis cells compared with chronic phase cells [30]. It is unclear to what degree and with how much hetero- or homo-geneity CML is addicted to these additional pathways.

Other proposed mechanisms affecting imatinib sensitivity include altered expression of drug influx and efflux proteins (i.e., Pgp and OCT-1) [31, 32], BCR-ABL gene amplification, and overexpression of BCR-ABL [33, 34]. In addition, many patients that develop imatinib resistance will not have a cause identified.

Response-based indicators of imatinib resistance

To ensure effective patient care in CML, the response to imatinib therapy is monitored frequently according to formally defined standards (Table 3) [35]. In this manner, resistance may be detected promptly and treatment changed, if appropriate. The National Comprehensive Cancer Network (NCCN) 2008 guidelines for CML recommend time-based landmark responses to treatment that should be met if the patient is to continue receiving the same imatinib schedule: a CHR should be achieved within 3 months, at least a minor cytogenetic response (Table 2) within 6 months, at least a MCyR within 12 months, and a CCyR within 18 months of treatment. If these landmarks are not met then a treatment change should be considered [35].

Results from the IRIS study underscore the importance of achieving such landmark responses. A retrospective analysis of outcomes of patients treated with imatinib in this trial, and those treated with interferon-a plus low-dose cytarabine in the CML91 trial demonstrated a significant survival advantage among patients who achieved a MCyR by 12 months, irrespective of the treatment administered [36]. Similarly, CCyR was found to be an independent predictor of survival and the key prognostic indicator in CML [8, 36, 37]. There are a number of prerequisites for gaining a CCyR. A hematologic response is a prerequisite for attaining a CCyR and also for long-term survival [38]. The degree of preceding cytogenetic response is also crucial. In the IRIS trial, the probability of eventually achieving a CCyR was only 15% if the karyotype at 6 months was >95% Ph chromosome-positive. Furthermore, if the response after 12 months of treatment was less

Table 3 NCCN monitoring guidelines for patients with CML receiving TKI therapy [35]

Time point of response	Monitoring measures
Diagnosis	• Bone marrow cytogenetics (or FISH analysis of peripheral blood)
	• Measurement of BCR-ABL transcript levels
During apparent response to therapy	• Measurement of BCR-ABL transcript levels every 3 months
	• Bone marrow cytogenetic analysis at 6 and 12 months, and at 18 months if CCyR not achieved by 12 months
At CCyR	• Measurement of BCR-ABL transcript levels every 3 months
	• Bone marrow cytogenetic analysis every 12–18 months in case of clonal abnormalities
Treatment failure, or during AP/BC stage CML	• BCR-ABL mutation analysis
Rising (≥1 log) BCR-ABL transcript levels	• Repeat measurement of BCR-ABL transcript levels in 1 month
	• Monthly measurement of BCR-ABL transcript levels, if rise confirmed
	• Consider BCR-ABL mutation analysis

than a MCyR, the probability of achieving a CCyR at 2 years was <20% [8]. In addition to the non-achievement of time-based landmark responses, loss of a previously achieved response or progression to advanced phase disease should also trigger a change in treatment [35]. It should also be noted that the NCCN provides criteria that define partial resistance and suggests that treatment should be reassessed in these cases, even in absence of outright failure (suboptimum responses). In such cases, the patient may continue to benefit from the current treatment schedule, but long-term outcome may improve under an alternative strategy.

Evidence is now emerging to suggest that time-based response landmarks earlier than those proposed by the NCCN are warning signs in patients unlikely to achieve long-term benefits from imatinib, in particular the failure to achieve an early cytogenetic or molecular response. For example, patients in the IRIS trial who did not achieve a CCyR with imatinib by 12 months had a significantly higher risk of disease progression than patients with such a response [7]. Equally, not achieving a cytogenetic response at 3 or 6 months was associated with lower overall survival and PFS compared with patients who reached these responses [37, 39–42]. A recent retrospective study has showed that not achieving a MCyR by 6 months is predictive of decreased overall survival [13]. Nevertheless, some patients without achieving a CCyR may have disease control for years. Long-term, prospective studies are needed to define the optimum cues for TKI changes in the absence of overt resistance or progression.

In terms of molecular response, patients who fail to achieve a 1-log reduction at 3 months, or a >2-log reduction by 6 months in BCR-ABL transcript levels are unlikely to subsequently achieve a substantial response and are at high risk for disease progression [24, 43]. Achievement of a MMR by 12 months appears to provide maximal protection from disease progression. Five-year follow-up data from the IRIS study revealed that no patient who achieved a MMR by 12 months had progressed to advanced disease [7]. Patients who had both a CCyR and MMR at 12 months of imatinib therapy had a 100% probability of remaining progression-free at 24 months as compared with 95% for patients who had a CCyR and a <3-log reduction of BCR-ABL transcripts, and 85% for patients who did not achieve a CCyR [44]. However, the degree of molecular response in patients already in CCyR is not associated with differences in survival outcome [13]. In contrast, a rise in BCR-ABL transcripts can serve as an early indicator of the development of resistance, but a single test showing an increase in transcripts should not prompt a change in treatment [21, 45–47]. Emergence of imatinib-resistant BCR-ABL mutations at any time during treatment is equivalent to a diagnosis of disease progression and should prompt a change in therapy [35].

Approved second-line TKI-based treatments: results from clinical trials in patients with imatinib-resistant or -intolerant CML

Patients who fail first-line imatinib therapy should be considered for a change in treatment. Current guidelines for CML provide three options: high-dose imatinib, dasatinib, or nilotinib [35]. Key factors that may influence the choice of agent used are given in Table 4.

High-dose imatinib

Some mechanisms of imatinib resistance may be overcome by dose escalating imatinib. Certain BCR-ABL mutations confer intermediate levels of resistance to imatinib [50, 51]. Imatinib resistance caused by BCR-ABL overexpression may also be overcome using higher doses of imatinib [52]. Studies have shown that dose escalating imatinib can

Table 4 Factors affecting the choice of second-line TKI for the treatment of CML [48, 49]

Agent	Contraindications	Boxed warnings	Key warnings and precautions	Key BCR-ABL mutations (resistance or low efficacy)
Imatinib	None	None	• Edema and fluid retention • Cytopenias • CHF, left ventricular dysfunction and cardiogenic shock • Hepatotoxicity • Hemorrhage • Bullous dermatologic reactions	>40; including P-loop (e.g., Y253F/H, E255 K/V), contact site (e.g., T315I), SH2 binding site, and A-loop
Dasatinib	None	None	• Myelosuppression • Bleeding related events • Fluid retention • QT prolongation • Interactions with H2 blockers and PPIs	T315I, F317L
Nilotinib	Patients with hypokalemia, hypomagnesemia, or long QT syndrome	QT prolongation and sudden deaths	• Myelosuppression • QT prolongation and sudden deaths • Elevated serum lipase • Hepatic function • Electrolyte abnormalities • Drug interactions • Food effects	T315I, P-loop mutations, F359

CHF congestive heart failure

induce responses in some patients who relapsed or were refractory to standard doses, with most benefit observed in patients who had suboptimal responses, while those who fail treatment rarely benefit [53, 54]. High-dose imatinib rarely results in deep, durable responses. Studies indicate that MCyRs are only gained by 26–38% of patients [53, 54]. Moreover, any responses gained are typically short-lived, best attained cytogenetic responses being soon lost by 43–50% of patients [54, 55]. Furthermore, almost all (93%) patients who do not achieve any cytogenetic response on standard-dose imatinib do not benefit from a high-dose regimen [53, 55]. Also, many patients were intolerant of high-dose imatinib and dose reductions were required in 41% of patients [53].

Dasatinib

Dasatinib overcomes most forms of imatinib resistance. It has activity against all BCR-ABL point mutations except T315I and unlike imatinib, dasatinib can bind multiple conformations of BCR-ABL and is a potent inhibitor of the SFKs associated with BCR-ABL-independent imatinib resistance [56, 57]. In contrast to imatinib, dasatinib is not a substrate for P-glycoprotein (Pgp) efflux pump, and OCT-1 does not significantly influence dasatinib uptake [58]. Dasatinib has 325-fold greater potency versus imatinib against BCR-ABL and therefore may also overcome imatinib resistance mediated by increased expression of BCR-ABL [33, 34].

Dasatinib has been assessed in a phase II development program: Src-ABL Tyrosine Kinase Inhibition Activity Research Trials (START). Four single-arm trials were initiated in adult patients with imatinib-resistant or imatinib-intolerant leukemias: START-C (CP CML), START-A (AP CML), START-B (myeloid BC CML), and START-L (lymphoid BC CML and Ph^+ALL). One prospective randomized trial, START-R, evaluated a dasatinib arm and a high-dose imatinib arm in patients who were previously resistant to standard-dose imatinib.

In patients with CP CML after 24 months of follow-up, dasatinib induced CHRs and MCyRs in 91 and 62% of patients, respectively [59]. Most MCyRs observed were complete cytogenetic remissions, observed in over half of patients (53%). MMRs were also achieved in 47% of patients [59]. With relatively limited follow-up responses seem to be durable. At 15 months, the PFS rate was 90, and 97% of patients who had achieved a MCyR maintained it up to this time point [60]. After a 24-month follow-up, PFS was 80% (75% in imatinib-resistant and 94% in imatinib-intolerant patients); 88% of patients who had achieved a MCyR having maintained it to this time point. Also at 24 months, OS was 94% (92% in imatinib-resistant and 100% in imatinib-intolerant patients) [59]. Dasatinib has also shown marked activity in patients with AP or BP CML [61, 62]. In patients with AP CML, the MCyR rate at 24 months was 40, and 61%

of patients achieving a MCyR maintained this response at 24 months. The median PFS was 19.5 months [63]. Though associated with a significantly lower response rate, deep and durable responses were also noted at 24 months in patients with BC CML [64]. But the majority of patients with BC CML do not have a sustained clinical benefit from dasatinib or other TKI-based therapy and should be considered for allogeneic stem cell transplantation.

The START-R study compared dasatinib with high-dose imatinib (800 mg/day) in patients with CP CML and resistance to imatinib 400–600 mg/day [65]. After 24 months of follow-up, dasatinib was superior to high-dose imatinib for rates of MCyR (53 vs. 33%; $P = 0.017$), CCyR (44 vs. 18%; $P = 0.003$), MMR (29 vs. 12%; $P = 0.028$), and PFS (86 vs. 65%; $P = 0.001$) [66]. Responses were also more durable in the dasatinib arm; 90% of patients receiving dasatinib maintained MCyR at 18 months compared with 74% of patients receiving imatinib [66].

In the START program, dasatinib demonstrated efficacy in patients with all imatinib-resistant BCR-ABL mutations tested, including P-loop mutations (where similar efficacy to wild type BCR-ABL is observed), except for T315 l [61, 62, 67]. In the START-R study, higher rates of MCyR were observed in both mutation-positive and mutation-negative patients receiving dasatinib as compared with those receiving high-dose imatinib. Furthermore, only dasatinib induced responses in patients with P-loop mutations [65]. A report evaluating response to dasatinib by baseline BCR-ABL mutation phenotype among patients enrolled in the START-C study confirmed activity across a range of mutants, including those in the P-loop, but also suggested that patients with F317L mutations may have diminished responses to dasatinib [68].

Dasatinib is generally well tolerated. Most adverse events (AEs) were grade 1–2 and resolved either spontaneously or with appropriate supportive care. Pleural effusions (all grades, 23%; grade 3–4, 5% at 70 mg BID; all grades, 10%; grade 3–4, 2% at 100 mg daily) and grade 3–4 cytopenias (neutropenia 46%, thrombocytopenia 41%, and anemia 18%) can occur with dasatinib. These AEs can usually be managed with dose interruption or reduction [48]. Additionally, diuretics and/or steroids (prednisone 20 mg po daily $\times 3$ days) and occasionally thoracentesis may be indicated in the management of dasatinib induced pleural effusions [35, 69]. Additionally, 10% of CP patients experienced hypophosphatemia in clinical studies [48]. There was no evidence of cumulative toxicity on long-term therapy [67]. As for all approved TKI treatments for CML, dasatinib is metabolized via the hepatic CYP3A4 cytochrome system. Care should therefore be taken when dasatinib is taken in conjunction with other agents that interact with this system.

Based on the data from the START program, dasatinib was approved for treated imatinib-resistant and -intolerant patients across all phases of CML (and Ph^+ALL) at a dosage of 70 mg twice daily. Results from a recent phase III dose-optimization study recently prompted a change in the recommended daily dose for patients with CP CML [70].

The rationale for performing the dose-optimization study derived from two clinical observations. First, in the phase I study of dasatinib, CHRs and MCyRs were achieved at total daily doses of 100 and 140 mg with both once daily and twice daily treatment regimens [71]. Second, the median delivered dose in the phase II program in CP CML patients was approximately 100 mg/day. It was therefore decided to compare once and twice daily regimens at total daily doses of both 100 and 140 mg. After a minimum follow-up of 6 months, similar response rates were seen across all four dasatinib arms (CHRs in 86–92%; MCyRs in 54–59%; CCyRs in 41–45%). PFS at 6 months was 92% for dasatinib 100 mg once daily and 89% for dasatinib 70 mg twice daily [70]. No significant difference was apparent between regimens also after a follow-up of 12 months (MCyRs in 56–63%) [70]. Twelve-month data also indicate that the 100 mg once daily schedule also has activity across all BCR-ABL mutations, except T315I.

Differences between regimens evaluated in the dose-optimization study were apparent, however, in terms of safety [70]. In the 100 mg once daily arm, there was a significantly lower frequency of grade 3–4 thrombocytopenia compared with the 70 mg twice daily arm (22 vs. 37%; $P = 0.004$). Frequencies of anemia, leukocytopenia, and neutropenia were also less, but these reductions were not statistically significant ($P > 0.05$). Pleural effusions (all grades) also occurred less frequently with dasatinib 100 mg once daily (7 vs. 16%; $P = 0.028$). Improved safety with the 100 mg once daily schedule was also reflected by the lower incidences of dose interruption (51 vs. 68%), reduction (30 vs. 55%), and discontinuation (16 vs. 23%) relative to the 70 mg twice daily schedule.

Results of this study demonstrate that, compared with the previously recommended 70 mg twice daily dose, a 100 mg once daily regimen offers a more favorable overall benefit–risk assessment in chronic phase CML. A separate trial in advanced phase patients showed that a once daily dose had a better safety profile with similar response rates; however, further follow-up is necessary before a change in treatment practice can be recommended [72]. The current prescribing information for dasatinib now recommends regimens of 100 mg once daily for the treatment of CP CML and 70 mg twice daily for the treatment of AP or BC CML, and Ph^+ALL [48].

Nilotinib

Nilotinib is an analog of imatinib, 10- to 50-fold more potent than its parent compound against BCR-ABL, which has recently been approved for the treatment of patients with CP or AP CML who have failed prior treatment. In vitro evidence shows that nilotinib has activity against all imatinib-resistant BCR-ABL mutations except T315 l, but that activity against P-loop mutations and other imatinib-resistant mutations, including F359C, may be diminished [56, 73]. Inhibitory plasma concentrations of nilotinib can usually be obtained for the majority of P-loop mutations and further in vivo evidence is needed.

Second-line nilotinib 800 mg/day has been assessed in an open-label phase II trial in patients with CP CML [74]. After 18 months of follow-up, CHRs were achieved in 85% of patients, MCyRs in 57%, and CCyRs in 41%. In total, 84% of patients who achieved a MCyR maintained it for 18 months [75]. A time to progression analysis showed that 64% of patients had not progressed at 18 months [75]. The overall survival rate at this time point was 91% [75]. These results are similar to those seen with dasatinib in the START-C trial.

Activity of nilotinib 800 mg/day in patients with AP CML was demonstrated in a phase II study [76]. After a follow-up of at least 12 months, MCyRs were achieved in 31% of patients [77]. At 12 months the percentage of patients who were progression-free was 57%, and the overall survival rate was 81%.

In the pivotal phase II study in patients with CP CML, nilotinib showed activity in patients harboring many imatinib-resistant BCR-ABL mutations (except T315I), and also in patients with resistance not associated with BCR-ABL mutations [74]. However, a sub-analysis of this study of the occurrence of baseline BCR-ABL mutations and their effect on treatment outcome after 12 months of treatment showed that no patient with Y253H, E255 K/V, or F359C/V mutations achieved a CCyR; though the number of patients with each mutation is relatively low, making definitive conclusions difficult [64]. These findings were supported in evaluations of patients enrolled in phase II clinical studies of nilotinib, which also showed that Y253F/H, E255 K, and E255K/V mutations were associated with disease progression [78, 79]. The P-loop mutations Y253H and E255 K/V are also among those that most frequently develop during nilotinib treatment and are associated with disease progression [78, 80].

The AEs associated with nilotinib therapy are predominantly mild to moderate in severity [74]. The incidences of grade 3–4 thrombocytopenia and neutropenia were similar to that observed with the dasatinib 100 mg once daily [77]. Nilotinib's specificity for the ABL kinase and comparably minimal inhibition of c-KIT and PDGFR also alters its toxicity profile. Inhibition of PDGFR is thought to be the cause of the edema associated with imatinib and dasatinib therapy [81]. In clinical trials only 10% of patients taking nilotinib have had peripheral edema and none have had grade 3–4 events [82]. There is minimal cross-intolerance with imatinib, although approximately half (49%) the patients with hematologic intolerance to imatinib experienced a recurrence of the grade 3–4 hematologic event (mostly thrombocytopenia) during nilotinib therapy [83].

Notably, the prescribing information for nilotinib contains a black box warning regarding the risk of QTc prolongation and sudden death. It should be noted that prolongation of QTc occurs with both imatinib and dasatinib, although sudden death was not observed with these agents in clinical trials.

QTc prolongation was observed on clinical studies with nilotinib and sudden deaths occurred that were believed to be related to ventricular repolarization abnormalities. If QTc prolongation does occur, treatment should be interrupted; dose reductions or discontinuation may also be necessary. Additionally, as with all ABL TKIs concomitant medication should be reviewed [82].

Nilotinib treatment may also be associated with biochemical abnormalities. Increases in serum lipase, bilirubin, alanine or aspartate aminotransferases, and alkaline phosphatase have been reported [82]. If these AEs occur, treatment should be withheld until serum levels return to grade $\leq$1. Treatment can then be resumed at a reduced dosage (400 mg/day). Hyperglycemia and electrolyte abnormalities [i.e., hypophosphatemia (10%), hypokalemia (1%), hyperkalemia (4%), hypocalcemia (1%), and hyponatremia (3%)] can also occur with nilotinib [82]. However, these electrolyte abnormalities may also occur with dasatinib in a similar proportion of patients [48, 82]. The prescribing information for nilotinib also carries contraindications for hypokalemia and hypomagnesemia due to these abnormalities potential worsening of QTc prolongation [82]. Nilotinib, like imatinib and dasatinib, is metabolized via the hepatic CYP3A4 cytochrome system, and caution should be taken when dasatinib is administered in conjunction with other compounds which interact with this system.

When to switch from imatinib to second-line TKI

Data from clinical trials has demonstrated that second-line TKIs are most effective in extending survival when administered in CP rather than in the advanced phases of CML. Three-year survival rates for imatinib-resistant patients decrease as a function of disease status; 72% for CP, 30% for AP, and 7% for BC [12]. Furthermore, PFS was improved when dasatinib was used upon loss of

cytogenetic response during imatinib treatment versus loss of hematologic response [84]. Current consensus guidelines recommend switching from imatinib to a second-generation TKI if (1) a CHR is not achieved by 3 months, (2) no cytogenetic response by 6 months, (3) minor or no cytogenetic response is achieved by 12 months, (4) a partial cytogenetic response is not achieved by 18 months, or (5) on disease progression to AP or BC CML.

Use of second-line TKIs in the first-line

Given the clinical benefit gained with dasatinib and nilotinib following imatinib failure, the possibility arises that earlier and deeper responses could be achieved with first-line use. Current evidence demonstrates that responses in patients with CP CML are greater than those in patients with advanced disease [12]. Moreover, patients in late CP are at greater risk of progression than patients with early CP CML. The contribution of BCR-ABL mutations during therapy is also an important issue as genetic instability increases with progression, making the disease more difficult to treat. As second-line agents are effective against a larger spectrum of BCR-ABL mutations than imatinib, the emergence of resistance may decrease if these agents are used earlier. Two clinical trials based at the M.D. Anderson Cancer Centre in Houston, Texas are currently evaluating first-line therapy with these agents. Early data for a small number of patients are available.

First-line dasatinib (100 mg/day) administered on a once- or twice-daily regimen is being investigated ($n = 40$; accrual ongoing) [85]. Preliminary results show that CCyRs were achieved in 94% of patients at 6 months, and in all evaluable patients (100%) at 12 months. Nilotinib 800 mg/day elicited similar activity [86]; CCyR rates at 6 and 12 months were 100%. Both drugs elicited significantly ($P < 0.001$) deeper responses at these time points than imatinib (historical controls) [85, 86]. Marked superiority over imatinib in this setting can also be demonstrated by comparing the response rates discussed above with those obtained for first-line imatinib in the IRIS study; after 18 months of follow-up in this trial the CCyR rate was 74% [9]. But until these trials are reported with sufficient follow-up, imatinib remains the standard of care for the first-line management of CP CML.

Third-line tyrosine kinase inhibitors

Resistance and intolerance to currently approved agents have necessitated the development of further compounds for the treatment of CML. Of note, there is a particular need for agents that are active in patients carrying the T315I BCR-ABL mutation, which is resistant to imatinib and both second-line TKIs [56]. Selected major developments are discussed below; a comprehensive review is beyond the scope of this article.

Bosutinib (SKI-606) inhibits both BCR-ABL and Src, being 10- to 20-fold more potent against BCR-ABL than imatinib in vitro, but has no activity against the T315I mutation [87, 88]. From preliminary data from a study in imatinib-resistant patients with CP CML, CCyRs were achieved by 30% of patients [89]. Activity in advanced stage CML and Ph^+ALL has also been demonstrated [90]. A phase III comparison of bosutinib and imatinib in newly diagnosed patients with CML is currently in recruitment.

INNO-406 is another dual BCR-ABL and SFK inhibitor, 55-fold more potent than imatinib in vitro, but also has no activity against T315I [91]. However, activity including CCyRs has been observed in an ongoing phase I dose-finding study in patients with CML (any phase) or Ph^+ALL resistant or intolerant to first- or second-line treatment, including dasatinib or nilotinib [92]. Aurora kinase inhibitors are a new class of compound that may provide successful treatment for patients with T315I-mutated CML. PHA-739538 is an aurora kinase inhibitor with strong antiproliferative activity against CD34+ cells taken from untreated CML patients and also from imatinib-resistant patients, including those with T315I [93]. A phase II study in patients with CML is now in progress [94]. Seven patients are currently enrolled, six of whom have T315I mutations. To date, two patients with T315I mutations have achieved cytogenetic responses, one of them a CCyR. The development of another aurora kinase inhibitor, MK-0457, was recently stopped following concerns over cardiotoxicity. Omacetaxine mepesuccinate (homoharringtonine; HHT) is a multi-targeted protein synthase inhibitor. This compound is currently in phase II development in imatinib-resistant patients with CML (all phases) and who carry T315I-mutated BCR-ABL [95]. To date, 29 patients have been enrolled, 17 of which have CP CML. Preliminary data indicate a CHR rate of 45% in CP CML patients. Cytogenetic responses have been reported in 27% of patients with CP CML; two responses were CCyRs. Reversion of T315I status in some patients has also been observed.

Finally, the addition of rapamycin to current TKI therapy may constitute a novel approach to the treatment of patients with refractory disease. The mammalian target of rapamycin (mTOR) is constitutively activated in BCR-ABL-transformed cells, and rapamycin inhibits the growth of CML cells obtained from patients with imatinib-resistant disease [96]. Recently, hematologic activity for this compound has been demonstrated in leukemic patients [97].

Conclusions

Targeted therapy with TKIs has dramatically changed the prognosis for patients with CML. Despite the impressive activity of imatinib, resistance to this therapy has become a significant clinical issue. Dasatinib and nilotinib are both effective in patients following imatinib failure or intolerance. High-dose imatinib may be effective in some patients following resistance to standard-dose imatinib, but dasatinib has been shown to be more efficacious. Careful consideration should be taken when deciding which TKI to select following imatinib failure. Currently, there is no definitive evidence for the superiority of either dasatinib or nilotinib in CP or AP CML. Dasatinib is the preferred agent in BC CML. Treatment decisions should be directed by both efficacy and safety parameters (Table 4). In particular, based on pre-clinical and clinical data, patients with certain P-loop mutations such as Y253F, E255V, and F359 may respond better to dasatinib; in contrast, patients with the point mutation F317L may respond better to nilotinib. Patients at risk for complications from fluid retention may be better suited to nilotinib. For each of these second-line TKIs, it may be more beneficial to administer them earlier in the disease course in order to minimize the emergence of resistance and improve the overall duration of response. Trials are currently underway to evaluate this hypothesis.

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